Reprod Med Biol (2015) 14:123–129
DOI 10.1007/s12522-015-0204-x

ORIGINAL ARTICLE

Insulin resistance in nonobese Japanese women with polycystic ovary syndrome is associated with poorer glucose tolerance, delayed insulin secretion, and enhanced insulin response

Hiroaki Negishi[1] · Kazuki Nakao[1] · Michiko Kimura[2] · Hiroshi Takenaka[1] · Michiharu Horikawa[1]

Received: 23 October 2014 / Accepted: 2 March 2015 / Published online: 19 March 2015

Abstract
Purpose To determine the prevalence of insulin resistance (IR) and impaired glucose tolerance (IGT) in PCOS patients, the optimal screening method, and to compare our findings between nonobese and obese Japanese women with PCOS.
Methods Ninety-eight PCOS patients were included in this research from 2006 to 2013. Glucose tolerance test (OGTT) was performed. Serum glucose and insulin concentration were assayed before and 30, 60, and 120 min after taking 75 g of glucose.
Results All examined metabolic parameters were significantly favorable in the nonobese subjects, below 25 kg/m^2. HOMA-IR, fasting insulin, glucose$_{120}$, and insulin$_{120}$ showed strong correlations with BMI. A total of 1.4 % of nonobese women had IR based on fasting insulin or HOMA-IR. However, 15.5 % (11/71) of nonobese women had IR as determined by a continuous increase of serum insulin level in OGTT. In comparison, the prevalence of IR among the obese women ranged from 41 to 59 %. AUC$_{glucose}$, glucose$_{60}$, glucose$_{120}$, and insulin$_{120}$ in nonobese women with a continuous insulin increase were higher than those without such a continuous increase.
Conclusions All examined metabolic parameters were significantly correlated with BMI. As the presence of a continuous increase of insulin level reflects to some degree poorer glucose tolerance, delayed insulin secretion, and enhanced insulin response compared with non-continuous insulin increase, OGTT might not been excluded to determine IR and IGT for nonobese women with PCOS.

Keywords Body mass index · Glucose tolerance test · HOMA-IR · Insulin resistance · PCOS

Introduction

Polycystic ovary syndrome (PCOS) occurs in about 10 % of women of reproductive age, making it one of the most common endocrine disorders in women [1]. Approximately 50–70 % of all women with PCOS have some degree of insulin resistance, and this hormone insensitivity probably contributes to the hyperandrogenism that is responsible for the signs and symptoms of PCOS. Although uncertainty on this issue exists, early detection and treatment of insulin resistance (IR) in this population could ultimately reduce the incidence or severity of diabetes mellitus, dyslipidemia, hypertension, and cardiovascular disease. Even if that proves to be the case, there are still several problems with our current approach to insulin sensitivity assessment in PCOS, including the apparent lack of consensus on what defines PCOS and "normal" insulin sensitivity.

The objectives of this study were to determine the prevalence of IR and IGT in PCOS patients and to compare our findings between nonobese and obese Japanese women with PCOS.

✉ Hiroaki Negishi
h_negishi@kiyosenomori.com

[1] Women's Clinic Ooizumigakuen, Higashi-oizumi 1-27-19, Nerima-ku, Tokyo 178-0063, Japan

[2] Department of Obstetrics and Gynecology, Saitama Medical College, Morohongou 38, Moroyama Town, Iruma-gun, Saitama 350-0495, Japan

Materials and methods

Participants

We recruited PCOS patients who were infertile and required drugs such as clomifene citrates or injections of follicle-stimulating hormone because of ovulation disorder. Ninety-eight patients were included in this study, after providing informed consent, from 2006 to 2013. Seventy-one subjects had BMI <25 kg/m^2 and 27 subjects had BMI ≥25 kg/m^2. The diagnosis of PCOS was followed the PCOS criteria of the Japanese Society of Obstetrics and Gynecology [2]: (1) the presence of oligoovulation and/or anovulation, (2) the characteristic appearance of polycystic ovaries on ultrasonography, and (3) excess androgen activity (elevated testosterone levels >5 ng/ml), or elevated luteinizing hormone (LH) levels with normal follicle-stimulating hormone (FSH) levels. Other etiologies (congenital adrenal hyperplasia, androgen-secreting tumors, Cushing's syndrome, and recovery phase of eating disorder) are excluded as a supplementary item.

Seventy-five-gram glucose tolerance test (OGTT) was performed. Serum glucose and insulin concentration were assayed before and 30, 60, and 120 min after taking glucose.

IR was defined as elevated fasting insulin (>15 μU/ml), elevated HOMA-IR (>2.5 μU mg/ml dl), or continuous increase of serum insulin level in OGTT. An abnormal ratio of glucose insulin was defined as (1) fasting glucose/fasting insulin <7.2 [3] and (2) glucose$_{120}$/insulin$_{120}$ ≤1.0 [4]. Impaired glucose tolerance (IGT) was defined as elevated fasting glucose (110 mg/dl ≤ fasting glucose ≤125 mg/dl) or elevated 2-h glucose (140 mg/dl ≤ glucose$_{120}$) [5]. Areas under the curve (AUC) for insulin and glucose were calculated by the trapezoid method.

Receiver operating characteristic (ROC) curves were constructed to describe the relationship between sensitivity and specificity for BMI in the prediction of IR. The board of our clinic approved this protocol, and all participants provided written informed consent.

Statistical analysis

Student's *t* tests were used to compare differences between various parameters when appropriate. Rates of abnormal values in the parameters were analyzed by the χ^2 test. Correlation coefficients were calculated by linear regression analysis. $p < 0.05$ was considered to indicate statistical significance.

Results

This analysis involved a comparison of two groups: nonobese (BMI <25 kg/m^2) and obese women (BMI ≥25 kg/m^2) with PCOS. Several background factors significantly differed between the two BMI groups (<25 and ≥25 kg/m^2) (Table 1). The nonobese BMI group was younger than the obese group: mean of 30 vs. 32 years old ($p < 0.01$). Serum testosterone level in the obese group was higher (0.67 ng/ml) than in the nonobese group (0.54 ng/ml, $p < 0.05$). There were no significant differences in nulligravid, serum LH and FSH levels, and LH/FSH ratio.

Table 2 shows that all examined parameters were significantly different between those with BMI below and above 25 kg/m^2, with all measures reflecting more favorable metabolism in the nonobese subjects.

AUC$_{glucose}$, AUC$_{insulin}$, HOMA-IR, fasting glucose, fasting insulin, glucose$_{120}$, and insulin$_{120}$ were significantly higher in the obese group than in the nonobese group. AUC$_{glucose}$/AUC$_{insulin}$, fasting glucose/fasting insulin, and glucose$_{120}$/insulin$_{120}$ were significantly lower in the obese group than in the nonobese group.

Correlation coefficients between metabolic variables and BMI are shown in Table 3. Every metabolic parameter had a significant correlation with BMI. In particular, HOMA-IR, fasting insulin, glucose$_{120}$, and insulin$_{120}$ showed strong correlations with BMI. Each parameter showed a correlation coefficient above 7.0 (0.72, 0.72, 0.71, and 0.72, respectively).

Table 1 Background of the patients stratified by body mass index

	Total Mean	$n = 98$ SE	BMI <25 kg/m^2 Mean	$n = 71$ SE	BMI ≥25 kg/m^2 Mean	$n = 27$ SE	p value
BMI	23.1	5.6	20.1	2.0	30.3	4.3	
Age, years	30.8	3.7	30.3	3.5	32.4	4.0	0.01
Nulligravid	63	64 %	49	69 %	14	52 %	NS
LH (mIU/ml)	10.3	4.9	10.7	4.9	9.2	4.9	NS
FSH (mIU/ml)	6.4	1.9	6.4	2.0	6.2	1.6	NS
LH/FSH	1.7	0.8	1.8	0.86	1.5	0.8	NS
Testosterone (ng/ml)	0.64	0.28	0.54	0.25	0.67	0.35	0.04

BMI body mass index, *SE* standard error, *NS* not significant

Table 2 Metabolic characteristics in women with polycystic ovary syndrome stratified by body mass index

	BMI <25 kg/m^2 Mean	$n = 71$ SE	BMI ≥25 kg/m^2 Mean	$n = 27$ SE	p value
$AUC_{glucose}$	12,826	2,516	176,001	4,659	2.17E−09
$AUC_{insulin}$	4,184	265	10,580	1,139	7.89E−12
$AUC_{glucose}/AUC_{insulin}$	3.65	0.18	2.35	0.29	0.000247
HOMA-IR (mg/ml dl)	0.92	0.06	2.92	0.30	1.65E−15
Fasting glucose (mg/dl)	81.6	0.76	90.6	2.1	2.03E−06
Fasting insulin (μU/ml)	4.5	0.3	12.9	1.3	1.38E−15
$Glucose_{120}$ (mg/dl)	92.7	2.5	141.5	8.5	4.76E−11
$Insulin_{120}$ (μU/ml)	35.4	2.9	114.0	13.8	1.61E−12
Fasting glucose/fasting insulin	21.9	1.1	10.0	1.5	5.23E−08
$Glucose_{120}/insulin_{120}$	3.5	0.2	1.7	0.2	5.56E−06

BMI body mass index, *AUC* area under the curve, $Glucose_{120}$ serum glucose level at 120 min in OGTT, $Insulin_{120}$ serum insulin level at 120 min in OGTT

Table 3 Correlation coefficients between metabolic variables and body mass index

		p value
$AUC_{glucose}$	0.63	1.02E−12
$AUC_{insulin}$	0.66	2.26E−14
$AUC_{glucose}/AUC_{insulin}$	−0.42	9.86E−06
HOMA-IR	0.72	3.7E−18
Fasting glucose	0.51	3.89E−08
Fasting insulin	0.72	5.14E−18
$Glucose_{120}$	0.71	2.46E−17
$Insulin_{120}$	0.72	9.83E−18
Fasting glucose (mg/dl)/fasting insulin (μU/ml)	−0.48	2.54E−07
$Glucose_{120}/insulin_{120}$	−0.47	5.82E−07

AUC area under the curve, *HOMA-IR* homeostasis model assessment insulin resistance index, $Glucose_{120}$ serum glucose level at 120 min in OGTT, $Insulin_{120}$ serum insulin level at 120 min in OGTT

Only one of the nonobese women with PCOS (1.4 %) had IR based on fasting insulin or HOMA-IR (Table 4). However, 15.5 % (11/71) of nonobese women with PCOS had IR as determined by changing of the serum insulin level in 75-g OGTT. In comparison, the prevalence of IR among the obese women ranged from 41 to 59 % depending on the method used to assess it: IR, HOMA-IR, or 75-g OGTT (40.7, 59.3, and 44.4 %, respectively). The highest HOMA-IR was 6.74 μU mg/ml dl with BMI of 34.2 kg/m^2. The lowest BMI for IR, HOMA-IR, and a continuous increase of serum insulin level in OGTT were 25.2, 23.3, and 17.6 kg/m^2, respectively.

Only one of 71 (1.4 %) of the nonobese women with PCOS had IGT ($glucose_{120}$ >140 mg/dl). On the other hand, 11 of 27 (41 %) of the obese patients had IGT. None of the nonobese women with PCOS had IGT based on the fasting blood glucose (fasting glucose >110 mg/dl) and only one of 27 (3.7 %) of the obese patients had IGT.

OGTT shows the differences in the mean serum glucose and insulin levels according to the two BMI groups. Note the increased yet parallel insulin response found in the obese BMI group. Glucose and insulin levels were higher at all time points in the obese group than in the nonobese group ($p < 0.01$). Serum insulin levels continued to increase during the time course in obese patients (data not shown).

In addition, ROC curves were constructed to examine BMI as a predictor of IR (Table 5). The sensitivity and specificity of escalating BMI were calculated and the resulting ROC curve produced. The cut-off point of BMI was calculated using the ROC curve, with the minimum distance to the point (0, 1) of each metabolic parameter. Area under the curve, cut-off point, sensitivity, and specificity are shown in Table 5. Cut-off points of fasting insulin >15 μU/ml, HOMA > 2.5 μU mg/ml dl, continuous insulin increase in OGTT, fasting glucose/fasting insulin <7.2, and $glucose_{120}/insulin_{120}$ <1.0 were 28.7, 26.7, 28.7, 25.2, and 28.7 kg/m^2, respectively.

Metabolic characteristics in nonobese women with PCOS were stratified by the presence or absence of a continuous increase of serum insulin level in OGTT (Table 6). $AUC_{glucose}$, $glucose_{60}$, $glucose_{120}$, and $insulin_{120}$ in nonobese PCOS women with the presence of a continuous increase of serum insulin level were higher than those in nonobese PCOS women without such an increase, in spite of the fact that HOMA-IR, fasting glucose level, and insulin level did not differ between them.

Discussion

Although the hyperinsulinemic-euglycemic clamp technique is the gold standard for assaying insulin sensitivity, it is too expensive, time-consuming, and labor-intensive to be

Table 4 Rates of abnormal values by body mass index

	BMI <25 kg/m^2	$n = 71$ (%)	BMI ≥25 kg/m^2	$n = 27$ (%)	p value
Fasting insulin >15 μU/ml	0	0	11	40.7	1.14E−08
HOMA-IR >2.5 μU mg/ml dl	1	1.4	16	59.3	1.33E−12
Continuous increase of serum insulin level in OGTT	11	15.5	12	44.4	0.003
Fasting glucose/fasting insulin <7.2	1	1.4	14	52	5.77465E−10
$Glucose_{120}/insulin_{120}$ <1.0	1	1.4	9	33	3.09256E−06
Fasting glucose >110 mg/dl	0	0	1	3.7	NS
200 mg/dl> $glucose_{120}$ >140 mg/dl	1	1.4	11	40.7	1.12E−07

BMI body mass index, *HOMA-IR* homeostasis model assessment insulin resistance index, $Glucose_{120}$ serum glucose level at 120 min in OGTT, $Insulin_{120}$ serum insulin level at 120 min in OGTT, *NS* not significant

Table 5 Receiver operating characteristic curve for body mass index as a predictor of insulin resistance

	AUC	Cut-off point	Sensitivity (%)	Specificity (%)
Fasting insulin >15 μU/ml	0.91	28.7	82	90
HOMA >2.5 μU mg/ml dl	0.94	26.7	90	95
Continuous increase of serum insulin level in OGTT	0.69	28.7	92	57
Fasting glucose/fasting insulin <7.2	0.92	25.2	85	93
$Glucose_{120}/insulin_{120}$ <1.0	0.92	28.7	87	75

AUC area under the curve, *cut-off point* of BMI is expressed as kg/m^2, *HOMA-IR* homeostasis model assessment insulin resistance index, $Glucose_{120}$ serum glucose level at 120 min in OGTT, $Insulin_{120}$ serum insulin level at 120 min in OGTT

Table 6 Metabolic characteristics in nonobese women with polycystic ovary syndrome stratified by the presence or absence of continuous increase of serum insulin level in OGTT

Continuous increase of serum insulin level	Positive Mean	$n = 11$ SE	Negative Mean	$n = 60$ SE	p value
Age, years	30.3	1.1	30.3	0.5	NS
HOMA-IR (mg/ml dl)	0.79	0.10	0.92	0.06	NS
BMI (kg/m^2)	19.6	0.8	20.2	0.3	NS
Fasting glucose (mg/dl)	81.1	1.5	81.6	0.9	NS
Fasting insulin (μU/ml)	3.9	0.5	4.5	0.3	NS
Fasting glucose/fasting insulin	24.5	3.7	21.8	1.2	NS
$Glucose_{30}$ (mg/dl)	125.4	9.9	125.9	3.3	NS
$Insulin_{30}$ (μU/ml)	25.4	4.3	43.8	3.4	0.035
$Glucose_{30}/insulin_{30}$	5.8	0.7	3.7	0.3	0.006
$Glucose_{60}$ (mg/dl)	136.3	10.4	108.1	4.0	0.010
$Insulin_{60}$ (μU/ml)	40.3	8.9	38.3	2.8	NS
$Glucose_{60}/insulin_{60}$	4.5	0.7	3.5	0.2	NS
$Glucose_{120}$ (mg/dl)	111.0	4.6	89.4	2.6	0.002
$Insulin_{120}$ (μU/ml)	49.0	9.3	31.2	2.2	0.008
$Glucose_{120}/insulin_{120}$	2.9	0.4	3.6	0.2	NS
$AUC_{glucose}$	14442.0	832.2	12546.6	311.7	0.027
$AUC_{insulin}$	4104.6	749.1	4041.5	243.4	NS
$AUC_{glucose}/AUC_{insulin}$	4.4	0.6	3.6	0.2	NS

BMI body mass index, *AUC* area under the curve, $Glucose_{30}$ serum glucose level at 30 min in OGTT, $Insulin_{30}$ serum insulin level at 30 min in OGTT, $Glucose_{60}$ serum glucose level at 60 min in OGTT, $Insulin_{60}$ serum insulin level at 60 min in OGTT, $Glucose_{120}$ serum glucose level at 120 min in OGTT, $Insulin_{120}$ serum insulin level at 120 min in OGTT, *NS* not significant

of practical use in an office setting. Homeostatic measurements, fasting glucose/insulin ratio, or homeostatic model assessment (HOMA) value and minimal model tests, particularly the oral glucose tolerance test (OGTT), represent the easiest office-based assessments of insulin resistance in PCOS patients. The OGTT is probably the best, simple, office-based method to assess women with PCOS because it provides information about both insulin resistance and glucose intolerance. The diagnosis of glucose intolerance holds greater prognostic and treatment implications. All obese women with PCOS should be screened for the presence of insulin resistance by looking for other signs of insulin resistance syndrome, such as hypertension, dyslipidemia, central obesity, and glucose intolerance.

There are still several problems with our current approach to insulin sensitivity assessment in PCOS. In spite of the fact that approximately 50–70 % of all women with PCOS have some degree of insulin resistance, the prevalence of abnormal fasting glucose/insulin ratio and HOMA-R in PCOS patients is unlikely to be so high in an office setting. All obese women with PCOS should be screened for the presence of insulin resistance. The need for OGTT screening is unclear because the identified prevalence of IR in lean PCOS patients contradicts what would be expected. Approximately 80 % of obese individuals among patients with PCOS, and approximately 40 % among non-obese individuals, have been reported to have some IR [6–9]. Indeed, even lean women with PCOS have elevated insulin resistance compared with BMI-matched controls [8]. On the other hand, some investigations reported that IR in those with BMI of less than 25 kg/m^2 was rare. Differences in the incidence of IR in PCOS patients have also been identified, among those with various eating habits, and in different ethnic groups, as well as in terms of the cut-off point used to define IR [10, 11].

Women with PCOS are known to be at some risk for IR, IGT, and type 2 diabetes mellitus. Currently, guidelines from the Androgen Excess Society recommend that a 2-h OGTT be performed on all obese women with PCOS [12]. This recommendation is based on the significant prevalence of IGT in obese women with PCOS and their increased risk of developing diabetes. Because of a lack of sufficient data on lean women with PCOS, these guidelines do not give a recommendation with regard to the assessment of IGT in lean women. Stovall et al. [10] reported that the incidence of IR was very low in lean women with PCOS using fasting insulin and HOMA-IR. Takeuchi et al. found that 52.9 % of lean Japanese women had an abnormal value by using $AUC_{insulin}$ in OGTT. They found that 19 % of lean women with PCOS had IR by using HOMA-IR [8 N11]. Our study showed that there was one identified case of IR (1.4 %) using HOMA-IR (>2.5) and fasting insulin (>15 μU/ml) in nonobese PCOS women; however, 15.5 % of nonobese women with PCOS had IR as determined using a continuous increase of insulin level in OGTT. Limited data have been provided on the effect of BMI on the compensatory insulin response, particularly in patients with normal body weight. Indeed, even lean women with PCOS were shown to have elevated insulin resistance compared with BMI-matched controls [8].

As regards insulin secretion, many studies have examined β-cell function in PCOS; however, thus far, the results have been equivocal. Studies have shown that there is a defect in glucose-stimulated insulin secretion [13–15], but other studies have found that insulin response is enhanced in women with PCOS, likely as compensation for the peripheral insulin resistance [16–18]. Manco et al. showed that young women with PCOS but normal glucose tolerance are able to compensate for severe insulin resistance with enhanced β-cell function. They are less insulin-sensitive but able to release much more insulin following glucose ingestion than age- and BMI-matched controls [19]. The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group proposed that future studies were necessary in nonobese women with PCOS to determine the utility of an oral glucose tolerance tests, although they may be considered if additional risk factors for insulin resistance, such as a family history of diabetes, are present [20]. Judging from our study, there was a good insulin response upon glucose loading in nonobese and obese PCOS women. Our study showed that 15.5 % (11/71) of nonobese PCOS women had a continuous increase of serum insulin level in OGTT. $AUC_{glucose}$, $glucose_{120}$, and $insulin_{120}$ in nonobese women with PCOS and IR were higher than in non-IR nonobese women with PCOS, in spite of the fact that HOMA-IR, fasting glucose, and insulin levels did not differ between them. This might suggest that glucose tolerance and insulin secretion at 30 min after glucose loading were poor in nonobese women with PCOS and IR compared with those in nonobese women with PCOS but without IR. In addition, judging from these findings, it might be worth carrying out OGTT for nonobese women with PCOS.

In Japan, approximately 30–40 % of women with PCOS are obese, which is a higher level of prevalence than the 7 and 15 % in the general population in those 20 and 30 years old, respectively [21], which almost corresponds with our data of 28 % (27/98). However, the incidence of obesity in Japanese women with PCOS is lower than in American and European women with PCOS, for whom the rate is more than 50 %. Therefore, it is important to screen for IR in nonobese Japanese women with PCOS. Again, OGTT for nonobese women with PCOS might be valuable to screen for IR in nonobese Japanese women with PCOS.

Our study showed that 15.5 % (11/71) of nonobese PCOS women had IR, based on a continuous increase of

serum insulin level in OGTT. $AUC_{glucose}$, $glucose_{120}$, and $insulin_{120}$ in nonobese PCOS women with IR were higher than in nonobese women without IR. In addition, $insulin_{30}$ was higher in women without IR than in those with IR and PCOS, in spite of the fact that HOMA-IR, fasting glucose level, and fasting insulin level did not differ between them. This might suggest that glucose tolerance was impaired and stimulation of insulin secretion by glucose was delayed; however, insulin response was enhanced as compensation for the peripheral insulin resistance in nonobese women with PCOS and IR compared with that in nonobese women with PCOS but without IR.

Long-term prospective studies are needed to determine the prognosis of nonobese women with PCOS, especially those with IR and PCOS. Several studies have revealed that metfolmin, insulin-sensitizer, treatment for nonobese PCOS improved the metabolic characteristics involving HOMA-R, fasting glucose and insulin levels, area under the curve of insulin response in addition to hyperandrogenism, menstrual irregularities [22–24], and pregnancy rate [25].

All of the women in this study underwent the ovulation induction including clomifene citrate with or without gonadotropins. Forty-five percent of non-obese women could ovulate by clomifene alone, the other women needed to add the gonadotropin injections to ovulate. Only one woman needed the laparoscopic ovarian drilling because of the poor response to clomifene and gonadotropin stimulation. The current systemic review with meta-analysis of randomized controlled trial showed the beneficial reproductive effects of metformin for PCOS patients [26]. Women with IR took metformin regardless of the value of BMI in our study (data not shown). The results were that 30 % of women with IR underwent clomifene intake and the other 62 % needed to add gonadotropin injection to get ovulation. Contrary, 51 % of women without IR could ovulate with clomifene intake alone and the other 49 % of women needed to add gonadotropin injections. There was no significant difference between women with IR and without IR, however, the rate of adding the gonadotropin injection to get ovulation tended to higher in IR group than in non-IR group.

In conclusion, all examined metabolic parameters were significantly more favorable in nonobese subjects and correlated with BMI. IR prevalence in nonobese women with PCOS was 0–16 %. This range of prevalence rates depends on the method of IR diagnosis: HOMA-IR, fasting glucose, or a continuous increase of serum insulin level in OGTT. As a continuous increase of serum insulin level reflects to some degree poorer glucose tolerance, delayed insulin secretion, and enhanced insulin response than a non-continuous insulin increase, OGTT might not been excluded to determine IR and IGT in nonobese women with PCOS, instead of HOMA-IR and fasting glucose level.

Acknowledgments The authors acknowledge the contributions of Rena Ishii, Rena Ikeda, Kumiko Kuroda, and Hisae Yokota for sample processing.

Conflict of interest H. Negishi, K. Nakao, M. Kimura, H. Takenaka, and M. Horikawa declare that they have no conflicts of interest.

Human rights statements and informed consent All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and its later amendments. Informed consent was obtained from all patients for being included in the study.

Animal rights This article does not contain any studies with animal subjects performed by any of the authors.

References

1. Randeva HS, Tan BK, Weickert MO, Lois K, Nestler JE, Sattar N, Lehnert H. Cardiometabolic aspects of the polycystic ovary syndrome. Endocr Rev. 2012;33:812–41.
2. Kubota T. Update in polycystic ovary syndrome: new criteria of diagnosis and treatment in Japan. Reprod Med Biol. 2013;12:71–7.
3. Kauffman RP, Baker VM, Dimarino P, Gimpel T, Castracane VD. Polycystic ovarian syndrome and insulin resistance in white and Mexican American women: a comparison of two distinct populations. Am J Obstet Gynecol. 2002;187:1362–9.
4. Radziuk J. Insulin sensitivity and its measurement: structural commonalities among the methods. J Clin Endocrinol Metab. 2000;85:4426–33.
5. Report of the expert committee on the diagnosis and classification of diabetes mellitus. Diabetes Care 1997;20:1183–97.
6. Carmina E, Koyama T, Chang L, Stanczyk FZ, Lobo RA. Does ethnicity influence the prevalence of adrenal hyperandrogenism and insulin resistance in polycystic ovary syndrome? Am J Obstet Gynecol. 1992;167:1807–12.
7. Dunaif A, Segal KR, Futterweit W, Dobrjansky A. Profound peripheral insulin resistance, independent of obesity, in polycystic ovary syndrome. Diabetes. 1989;38:1165–74.
8. Dunaif A. Insulin action in the polycystic ovary syndrome. Endocrinol Metab Clin North Am. 1999;28:341–59.
9. Ovalle F, Azziz R. Insulin resistance, polycystic ovary syndrome, and type 2 diabetes mellitus. Fertil Steril. 2002;77:1095–105.
10. Stovall DW, Amelia Purser Bailey AP, Lisa M, Pastore LM. Assessment of insulin resistance and impaired glucose tolerance in lean women with polycystic ovary syndrome. J Womens Health. 2011;20:37–43.
11. Takeuchi T, Tsutsumi O, Taketani Y. Abnormal response of insulin to glucose loading and assessment of insulin resistance in non-obese patients with polycystic ovary syndrome. Gynecol Endocrinol. 2008;24:385–91.
12. Salley KE, Wickham EP, Cheang KI, Essah PA, Karjane NW, Nestler JE. Glucose intolerance in polycystic ovary syndrome—a position statement of the Androgen Excess Society. J Clin Endocrinol Metab. 2007;92:4546–56.
13. Dunaif A, Finegood DT. Beta-cell dysfunction independent of obesity and glucose intolerance in the polycystic ovary syndrome. J Clin Endocrinol Metab. 1996;81:942–7.

14. Arslanian SA, Lewy VD, Danadian K. Glucose intolerance in obese adolescents with polycystic ovary syndrome: roles of insulin resistance and beta-cell dysfunction and risk of cardiovascular disease. J Clin Endocrinol Metab. 2001;86:66–71.
15. Ehrmann DA, Barnes RB, Rosenfield RL, Cavaghan MK, Imperial J. Prevalence of impaired glucose tolerance and diabetes in women with polycystic ovary syndrome. Diabetes Care. 1999;22:141–6.
16. Holte J, Bergh T, Berne C, Wide L, Lithell H. Restored insulin sensitivity but persistently increased early insulin secretion after weight loss in obese women with polycystic ovary syndrome. J Clin Endocrinol Metab. 1995;80:2586–93.
17. Morin-Papunen LC, Vauhkonen I, Koivunen RM, Ruokonen A, Tapanainen JS. Insulin sensitivity, insulin secretion, and metabolic and hormonal parameters in healthy women and women with polycystic ovarian syndrome. Hum Reprod. 2000;15:1266–74.
18. Vrbikova J, Grimmichova T, Dvorakova K, Hill M, Stanicka S, Vondra K. Family history of diabetes mellitus determines insulin sensitivity and beta cell function in polycystic ovary syndrome. Physiol Res. 2008;57:547–53.
19. Manco M, Castagneto-Gissey L, Arrighi E, Carnicelli A, Brufani C, Luciano R, Mingrone G. Insulin dynamics in young women with polycystic ovary syndrome and normal glucose tolerance across categories of body mass index. PLoS One. 2014;4(9):e92995.
20. The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. Fertil Steril. 2004;8:19–25.
21. Office for Life-Style Related Diseases Control. General Affairs Division, Ministry of Health, Labour and Welfare, Japan. The National Health and Nutrition Survey in Japan, 2009.
22. Tan S, Hahn S, Benson S, Dietz T, Lahner H, Moeller LC, Schmidt M, Elsenbruch S, Kimmig R, Mann K, Janssen OE. Metformin improves polycystic ovary syndrome symptoms irrespective of pre-treatment insulin resistance. Eur J Endocrinol. 2007;157:669–76.
23. Marcondes JA, Yamashita SA, Maciel GA, Baracat EC, Halpern A. Metformin in normal-weight hirsute women with polycystic ovary syndrome with normal insulin sensitivity. Gynecol Endocrinol. 2007;23:273–8.
24. Yilmaz M, Biri A, Karakoç A, Törüner F, Bingöl B, Cakir N, Tiras B, Ayvaz G, Arslan M. The effects of rosiglitazone and metformin on insulin resistance and serum androgen levels in obese and lean patients with polycystic ovary syndrome. J Endocrinol Invest. 2005;28:1003–8.
25. Kumari AS, Haq A, Jayasundaram R, Abdel-Wareth LO, Al Haija SA, Alvares M. Metformin monotherapy in lean women with polycystic ovary syndrome. Reprod Biomed Online. 2005;10:100–4.
26. Palomba S, Falbo A, La Sala GB. Metformin and gonadotropins for ovulation induction in patients with polycystic ovary syndrome: a systematic review with meta-analysis of randomized controlled trials. Reprod Biol Endocrinol. 2014;12:3.